REMARKS

Interview Summary

Applicants, Applicants' European counsel, and undersigned counsel thank the Examiner for discussing this case by telephone on September 4, 2008. During the interview, the prior art rejection was discussed in general terms. No agreement was reached during the interview.

Status of the Claims

Pending claims are 31-36.

Withdrawn claims are cancelled without prejudice, and claim 1 and claims depending from claim 1 are also cancelled without prejudice in order to narrow the remaining issues. All rights to prosecute the cancelled claims in later applications are reserved.

Claim 32 is amended for clarity.

Claim 31 is amended to specify that the modified mRNA encodes a human tumour antigen. Support is found in paragraphs [0051] on pages 14-15 and [0057] on page 18.

Support for claim 35 (reciting that the mRNA encodes a secretory leader) is found, e.g. at Example 3 at [0092].

Support for claim 36 (reciting formulation for injection) is found, e.g. at [0056].

No new matter has been added.

Rejections

Applicants acknowledge with appreciation that the rejection under 35 U.S.C. 112, first paragraph (lack of enablement) has been withdrawn.

Claims 1, 4, 6-9, 11-16, and 29-34 were newly-rejected under 35 U.S.C. 103, on the ground that the claimed subject matter would have been obvious from Felgner et al. (U.S. 5,580,859) in view of Chen et al. (WO 99/20774) and Fomsgaard (WO 00/29561). The rejection is respectfully traversed as to amended claim 31 and the claims which depend from claim 31.

The Subject Matter of the Amended Claims Would Not Have Been Obvious

The subject matter being claimed in this application is a composition which comprises a modified mRNA which encodes a human tumour antigen, wherein the mRNA has an increase in Guanine/Cytosine (GC) content relative to the GC content of the wild-type mRNA encoding the same antigen (herein "GC enriched mRNA").

The GC enriched mRNA compositions recited in claims 31-38 would not have been obvious for at least the following reasons:

i) the disclosure of the cited primary and secondary references relate to distinct technical subject matter, and their combination as proposed would not have made the invention obvious;

ii) the state of the art as a whole did not recognize a need to enrich the GC content of an mRNA encoding a human antigen for expression in a human system; and

iii) declaration evidence provided with this response supports a finding that GC enriched mRNA encoding a human tumour antigen is more effective for anti-tumour vaccination than is the corresponding wild-type mRNA, a finding which would not have been expected in view of the complexity and unpredictability associated with generating an anti-tumour response *in vivo*.

These points are addressed in turn.

The Cited References Cannot be Properly Combined to Find that the Subject Matter Would Have Been Obvious

As a preface to the discussion which follows, the disclosure of the cited references is summarized as it relates to the subject matter now being claimed.

The Felgner et al. patent teaches direct administration of DNA or RNA for therapy or immunization. Suggested modifications to the DNA or RNA are disclosed at Col. 12, lines 15-29 and Col. 24, line 30 - Col. 25, line 35, but there is no disclosure of enriching the GC content

of an mRNA (or of a DNA). Felgner et al. provide a prophetic suggestion to generate an *in vivo* T-cell immune response to a tumour antigen at Col. 21, lines 57-64, but Felgner et al. provide no disclosure which demonstrates a T-cell immune response to a tumour antigen *in vivo*, and no disclosure which demonstrates anti-tumour activity *in vivo*. Felgner's *in vivo* examples which indicate some type of immune response, and which are not prophetic, use the HIV proteins nef and gp120. See Examples 9 and 19. [1]

The cited Chen reference is narrowly focused upon a specific antigen - MSP-1 from the organism *P. falciparum* - which is reported to be particularly difficult to express in mammalian cell culture systems (i.e. page 2, lines 3-11). To address that problem, DNA encoding MSP-1 antigen is modified to reduce AT content and eliminate instability motifs and rare codons relative to the expression system. Page 3, lines 4-13. While Chen suggests a modified DNA vaccine, it is not demonstrated that administration of the modified DNA encoding MSP-1 is able to induce either a B cell response or a CTL response. No evidence is provided that GC enrichment has a therapeutic effect. There is no disclosure to administer an mRNA which encodes MSP-1 or to modify an mRNA which encodes MSP-1. There is no mention of a composition including an mRNA encoding a human tumour antigen (nor any suggesting to enrich the GC content of an autologous gene). The disclosure is not concerned with treatment of tumours.

The Fomsgaard reference discloses a DNA vaccine against HIV. To overcome the low expression and to render the expression *rev*-independent (page 1, last paragraph), a series of modifications is proposed. First, an HIV gene from an early isolate is cloned ("first nucleotide sequence"). From the first nucleotide sequence, the codons are optimized to mammalian highly expressed proteins, creating a "second nucleotide sequence." The second nucleotide sequence is modified to remove selected restriction sites ("third nucleotide sequence"). The third nucleotide sequence is modified to contain terminal restriction sites, and is further modified to introduce

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[1] Applicants note that genes from HIV are pathogenic proteins foreign to the vaccinated mice. As persons in the art are aware, the immune system is specialized to fight against pathogens. From Felgner's results, it would not have been apparent that an immune response would be generated against self antigens (tumor antigens are self antigens). Felgner's showing with respect to heterologous antigens does not provide any indication that an immune response could be generated against human tumor antigens.

"snuts"[2] into the sequence around certain regions and at the terminals, creating a "cassette" structure. Similar to Chen, there is no suggestion to enrich the GC content of an autologous gene. There is no mention of a composition including an mRNA encoding a human tumour antigen. The disclosure is not concerned with treatment of tumours.

The present claims require a composition which is characterized by containing a GC-enriched mRNA encoding a human tumour antigen. From the prior art, this subject matter would not have been obvious in the absence of motivation for the skilled worker to, first, select mRNA (as opposed to DNA), and then, to select mRNA encoding a human tumour antigen, and then, to modify the mRNA specifically by increasing the GC content of that mRNA. These selections - and the results obtained by making these selections (addressed *infra*) - would not have been obvious to the skilled artisan.

The most basic reason not to combine the cited references is that a skilled artisan reading Felgner et al. would be provided with only a prophetic suggestion that anti-tumour efficacy might be realized upon administering a nucleic acid vaccine, but is provided with no suggestion to use a modified mRNA which is GC enriched. The secondary references, on the other hand, are unrelated to anti-tumour therapy, and are directed solely to enhancing expression of particular antigens from particular pathogenic infectious agents. As pointed out above, neither secondary reference suggests modification of a nucleic acid encoding an autologous antigen. Since the technical problems being addressed by the secondary references have no direct and apparent connection to anti-tumour vaccination, the cited references when considered cumulatively do not reasonably suggest the claimed "pharmaceutical compositions," at least absent the hindsight provided by reading applicants' disclosure.[3]

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[2] A "snut" is defined at page 6, lines 2-5, as the nucleotide sequence comprising the minimal entity of the cassette system.

[3] An adequate showing of motivation to combine references requires "evidence that a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention would select the elements from the prior art references for combination in the manner claimed." *Ecolochem, Inc. v. Southern California Edison Co.*, 227 F. 3d 1361, 1375 (Fed. Cir. 2000), quoting *In re Rouffet*, 149 F. 3d 1350, 1357 (Fed. Cir. 1998). As the Supreme

The Usefulness of Enriching the GC Content of mRNA Encoding Human Antigens for Expression in Human Cells Was not Evident from the Existing State of the Art

Both Chen and Fomsgaard are concerned with enhancing expression of an antigen which is heterologous to the cellular environment where expression of the antigen is sought to be enhanced. In particular, the malarial antigen disclosed by Chen, and the HIV antigens disclosed by Fomsgaard, are heterologous to human cells.

In contrast, the claimed pharmaceutical compositions are characterized by containing mRNA encoding human tumour antigens for expression in a human host. It was not evident from the state of the art at the time of the invention that enrichment of GC content, or codon optimization, was an important factor when expressing a nucleic acid encoding a human antigen in a human host cell.

Subsequent to the filing date of this application, Robinson, et al., *PLoS ONE* 3(3):e1801, 2008 (copy attached) states:

> Despite the recognized variability in codon content of human genes ...little attention has been focused upon the possibility that expression of human proteins might be limited in human cells by the codon content of their mRNAs. On the contrary, there appears to have been a widespread tacit assumption that even though some human ORFs may have an unusually low G+C content in the wobble positions, the deviation from average is not so extreme as to restrict protein expression due to limiting cognate tRNA availability.

Robinson et al. *Discussion*, at paragraph bridging pages 6-7 (footnotes and citations omitted).

Specifically concerning *in vivo* expression, Robinson et al. state:

Court has recently reminded: "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *KSR v. Teleflex*, 127 SCT 1726, 1742 (2007).

> Our experiments were based upon overexpression by transient transfection, and *in vitro* translation. The extent to which codon bias influences gene expression *in vivo* remains an open question.

Robinson et al. *Discussion*, at paragraph bridging cols 1-2 on page 9.[4]

Robinson et al. noted, in the first of the two passages quoted above, that "little attention" has been focused upon the possibility that expression of human proteins might be limited in human cells by the codon content of their mRNAs. Robinson et al. go on to note:

> In one of the few exceptions, overexpression of human erythropoietin in mammalian cells was shown to be influenced by engineering to contain human (high G + C) or yeast (high A + T) optimized codons, although expression levels differed by only 2.5-fold [49]. Our data demonstrate that intra-gene codon bias can have substantially greater effects upon protein expression within cells of the same organism.

Robinson, page 7, first column - 2d column.

A close review of reference [49] cited by Robinson - namely, Kim et al., Gene, 199:293 (1997) (copy enclosed) - reveals that even the rare "exception" does not teach towards the presently-claimed subject matter.

Kim et al. compared the expression from several erythropoietin (EPO) constructs, having human or yeast codon usage or a hybrid of both, which were expressed transiently in 293T cells. Page 294, 2d column. Significantly, there was no comparison reported between expression of human wild-type EPO as compared to human-codon optimized EPO. Moreover, comparison of the different constructs suggested that at least the promoter-proximal region should not be modified. It was found that decreasing the GC content downstream of the initiator codon resulted in improved EPO expression. Page 298, 2d column. This disclosure teaches away from enriching GC, at least in promoter-proximal portions of the molecule, and at a minimum creates

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[4] Applicants note that this passage suggests uncertainty associated with improved *in vivo* expression even if improved *in vitro* expression has been demonstrated. As it relates to the present claims, an observation that increased expression would be expected (page 7 of the Official Action, lines 3-15) does not correlate necessarily to an expectation of increased *in vivo* expression or to achieving any *in vivo* biological effect.

unpredictability as to the effects which GC content modification of nucleic acids encoding human antigens would be likely to produce.

For these additional reasons, the claimed compositions would not have been obvious.

GC Enriched mRNA Encoding Human Tumour Antigens is More Active In Vivo to Slow Tumour Growth than the Corresponding Wild-Type mRNA

Submitted with this response is the Second Declaration of Dr. Ingmar Hoerr. In this declaration, Dr. Hoerr reports experiments which compared the activity of GC-enriched mRNAs encoding certain human tumour antigens to the activity of the corresponding wild-type mRNAs, using two different assay formats which are predictive of anti-tumour utility.

Specifically, the declaration shows that, in tumour challenge experiments, tumour growth was reduced more efficiently by vaccination with GC-enriched mRNA as compared with the respective wild type mRNA coding for the human tumour antigens Survivin, GP100 and TRP-2.[5]

Further experiments reported in the declaration are "ELISPOT" experiments. The ELISPOT experiments showed that vaccination of animals with GC-enriched mRNA coding for the human tumour antigens MAGE-A2, MAGE-C2 and STEAP led to the induction of more tumour antigen specific cytotoxic T- cells than did vaccination with wild-type RNA. This is significant since a correlation is known to exist between the generation of tumour antigen-specific cytotoxic T-cells and the induction of immunity against tumour cells.

These results would not have been predictable. First, at a general level, *in vivo* expression is not necessarily predictable from *in vitro* expression, as noted earlier. Second, therapeutic efficacy is not predictable from *in vivo* expression. More particularly in relation to claims 31-38, however, achieving an actual anti-tumour response *in vivo* in an animal is

[5] As Dr. Hoerr notes, there is no human model for assessing anti-tumour activity, and the use of the mouse system described in the declaration, which involves introducing tumour cells which express human tumour antigens into mice, is an art-recognized experimental model.

inherently complex and unpredictable.[6] Due to this unpredictability, the improved anti-tumor response *in vivo* achieved using GC enriched mRNA coding for tumor antigens was unexpected, even assuming that improved *in vitro* expression could have been expected (which applicants do not concede for the reasons mentioned above). For this reason, applicants respectfully traverse the reasoning in the Official Action that the invention would have been obvious based simply upon a perceived expectation of "increasing the expression of the antigenic protein." (Official Action, page 7).

As noted, the disclosure of Felgner et al. of anti-tumour utility is speculative. The Felgner et al. disclosure does not put the public into possession of useful information relative to embodiments directed against human tumour antigens. For this further reason, Felgner's disclosure should not be combined with Chen or Fomsgaard with a reasonable expectation of achieving useful anti-tumour compositions.[7]

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[6] From a technical standpoint, the unpredictability of the subject matter should take into account the hurdles which must be overcome to achieve effective anti-tumour response by vaccination. For example, 1) the mRNA must enter the target cells without being digested in the extracellular space; 2) uptake of mRNA is a process which is not understood in detail. If the mRNA is incorporated by endosomes, the amount of protein which is expressed depends on the amount of mRNA which can escape from endosomes; 3) the immune response which is induced by the encoded protein depends on the cell type which uptakes the mRNA. If the cells express MHC I molecules they can induce a cytotoxic T cell response, and if they express MHC II molecules they can induce a TH1- or TH2 response (which includes a B-cell response); 4) tumour antigens are self-antigens, and it is necessary to overcome the tolerance of the immune system, which normally does not recognize self-antigens; 5) induction of an immune response does not alone ensure that the immune system is able to inhibit tumour growth. Although it is known that a cytotoxic T cell response plays an important role, the responsible mechanisms are not fully elucidated.

Under *KSR International Co. v. Teleflex Inc.* 127 S.Ct. 1727 (2007), the obviousness analysis (in situations where elements from different prior art references are being combined) is focused upon predictability. *KSR* states: "The combination of familiar elements is likely to be obvious when it does no more than yield predictable results." *KSR*, 127 S. Ct. at 1739. The treatment of cancers is normally considered to be an unpredictable art. See, e.g. *Ex Parte Germain Fuh*, 2002 WL 31234529 (Bd. App. Int. 2002) ("The treatment of cancers, such as breast cancer, is an unpredictable art.").

[7] The rationale being offered in this argument, and elsewhere in the current response, addresses the cumulative teachings of the cited references and is not limited to attacking the

In summary, it would not have been predictable at the time of the invention that the modified mRNA compositions being claimed would be active as vaccines *in vivo* and that they would be more effective to slow tumour growth *in vivo* than unmodified (wild-type) mRNA encoding the same tumour antigens. The cited prior art, considered alone or in proper combination, does not reasonably suggest that GC enrichment of mRNA encoding human tumour antigens - which are autologous antigens to humans - would provide enhanced anti-tumour utility *in vivo*.

Accordingly, the claimed pharmaceutical compositions would not have been obvious to one of ordinary skill in the art, and Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 103.

In the Official Action (pages 7-9) claim 10 was separately rejected, but no comment on that rejection is considered to be necessary since claim 10 has been cancelled in this response.

CONCLUSION

In view of the foregoing remarks, Applicants believe the pending claims define a patentable advance in the art, and accordingly, the present claims are in condition for allowance. If any issues remain which might be facilitated by telephone conference, the Examiner is invited to contact the undersigned at the number provided below.

Favorable action on pending claims 31-36 is requested.

Also attached please find a Power of Attorney by the assignee of record. The previous Power of Attorney was to the same law office (Connolly Bove Lodge & Hutz LLP) but to a different branch office having a different customer number.

Applicants attach a petition for a three-month extension of time. No additional claim fee is believed to be due (28 claims have been paid for previously). However, if any additional fee is

disclosures of the references individually. C.f., "Response to Arguments - 35 USC § 103" on pages 9-10 of the Official Action.

due, please charge our Deposit Account No. 03-2775 under Order No. 22122-00009-US1 from which the undersigned is authorized to draw.

Dated: October 14, 2008

Respectfully submitted,

Electronic signature: /Robert G. McMorrow, Jr./
Robert G. McMorrow, Jr.
Registration No.: 30,962
CONNOLLY BOVE LODGE & HUTZ LLP
1007 N. Orange Street
Wilmington DE 19899
Attorney for Applicant
(302) 658-9141

Encl: 1) Robinson article
2) Kim article
3) Second Declaration of Dr. Ingmar Hoerr
4) Power of Attorney by the assignee
5) Change of Correspondence Address
6) Petition for Extension of Time